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PATENT SPECIFICATION

745,069

Date of filing Complete Specification: March 26, 1954.

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Complete Specification Published: Feb. 22, 1956.

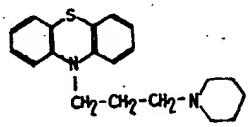
Index at acceptance:—Class 2(3), B4(A4:E), C(1A16:3C10).

COMPLETE SPECIFICATION

Improvements in or relating to Phenthiazine Derivatives and to their production

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new phenthiazine derivatives and to processes for their production. The new phenthiazine derivatives of the present invention are 10-(3¹-pyrrolidino-propyl)-phenthiazine which has the formula:



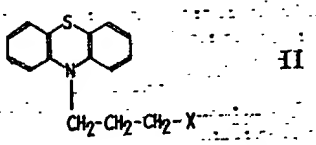
I

and its salts, including its quaternary ammonium salts.

According to features of this invention, the aforesaid new phenthiazine derivatives are prepared by

(a) heating a 1-pyrrolidino - 3 - halogenopropane (in the form of the base or a salt thereof) with phenthiazine. This condensation may be carried out without a condensing agent by the action of a solution, for example in xylene, of the 3-pyrrolidino-1-halogenopropane base on phenthiazine, if desired by heating under superatmospheric pressure. It is however, preferred to operate in the presence of an alkaline condensing agent, e.g. an alkali metal or derivative thereof such as the hydroxides, hydrides, amides or alcoholates, and more particularly sodium hydroxide or sodamide, in solution in an organic solvent, (e.g. toluene or xylene) at the boiling point of the solvent.

(b) heating pyrrolidine with a phenthiazine of the formula:



II

in which X represents the acid residue of an alkyl ester known to be active as an alkylating agent, e.g. a halogen atom or the residue of a sulphonic or sulphuric ester.

(c) cyclising 2-bromo-2¹-(3¹¹ - pyrrolidino-propyl)-amino-diphenylsulphide by heating it in an anhydrous solvent in the presence of an acid-binding agent. Preferred solvents are the N-substituted amides of fatty acids containing not more than 3 carbon atoms, e.g. dimethyl formamide and N-methylacetamide, of which the former is preferred. The cyclisation is conveniently brought about by refluxing the reaction mixture. As the acid-binding agent, it is preferred to employ potassium carbonate or sodium carbonate; however other agents such as caustic soda can also be used. In some cases (such as when an alkali carbonate is employed) the reaction can be accelerated by means of a dehydro-halogenation catalyst such as copper powder.

The following Examples will serve to illustrate the invention but are not to be regarded as limiting it in any way:—

EXAMPLE I

A solution of 3-pyrrolidino-1-chloropropane (23.6 g.) in xylene (50 c.c.) is run gradually over a period of ½ hour with agitation into a mixture of phenthiazine (26.5 g.), sodamide (85%; 7.8 g.) and xylene (100 c.c.); heated to 110° C. When the addition has been completed, heating is continued for a further 2 hours at about 140° C. After cooling, the reaction mixture is treated with water (200 c.c.) and made acid to methyl

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orange with hydrochloric acid (d=1.16; 25 c.c.). The xylene layer is separated and the aqueous layer is extracted with ether (100 cc.) The ether is decanted and the aqueous layer is then made alkaline to thymolphthalein with sodium hydroxide (d=1.33; 25 cc.). The base is extracted with ether (3×100 cc.). The ethereal solution is dried over sodium sulphate, the ether is evaporated on the water-bath and the residue is distilled. 10-(3¹-pyrrolidino-propyl) - phenthiazine (35 g.) is thus obtained which boils at 210—220° C. under 0.45 mm. of mercury. By treating the base dissolved in acetone with an acetone solution of oxalic acid, the acid oxalate is obtained which melts at 198° C. (Kofler). By treating the base dissolved in acetone with methyl iodide, the iodomethylate is obtained which, after recrystallisation from alcohol, melts at 196—198° C. (Kofler).

EXAMPLE II.

A mixture of 10-(3¹-chloro-propyl)-phenthiazine (4.53 g.) (prepared for example by the method of Gilman and Shirley Am. Soc. *66* 890 (1944)), pyrrolidine (2.34 g.) and toluene (30 cc.) is heated at 100° C. for 17 hours in a sealed tube. After cooling, the mixture is dissolved in water, acidified to Congo red with dilute sulphuric acid and extracted with ether. The aqueous layer is separated and made alkaline by the addition of an excess of dilute caustic soda. The base which separates is extracted with ether. The ether is driven off and the product is distilled. The 10-(3¹-pyrrolidino-propyl) - phenthiazine described in Example I is thus obtained.

EXAMPLE III.

2 - Bromo-2¹-amino - diphenylsulphide (28 g.) and 1-chloro-3-pyrrolidino-propane (17.7 g.) are heated under reflux for 3 hours with sodamide (3.9 g.) in anhydrous xylene (370 cc.).

After cooling, the reaction mixture is washed with water (200 cc.). After the addition of water (600 cc.), the mixture is extracted with normal hydrochloric acid (100 cc. and then 50 cc.). The acid extracts are made alkaline with 10N caustic soda (16 cc.). The base which precipitates is extracted with ether (3 lots of 100 cc.). The ethereal solution is dried over sodium sulphate, the ether is driven off on a water bath and the residue is distilled. 2-Bromo - 2¹-(3¹¹ - pyrrolidino-propylamino)-diphenylsulphide (17 g.) in the form of oil boiling at 214—230° C. under 0.4 mm. of mercury is obtained.

A solution of 2-bromo-2¹-(3¹¹-pyrrolidino - propyl-amino) - diphenylsulphide (15 g.) in dimethylformamide (130 cc.) is heated under reflux for 4 days with potassium carbonate (8 g.) and powdered copper (0.7 g.). After cooling, the insoluble mineral substance is filtered off and the filtrate is diluted with water (350 cc.) and extracted with ether (3 lots of 70 cc.). The ethereal extracts are dried over sodium sulphate, the ether is driven off on the water bath and the residue is distilled. The 10-(3¹-pyrrolidino-propyl)-phenthiazine thus obtained boils at 210—219° C. under 0.5 mm. of mercury. Its oxalate melts at 197—198° C.

The 2 - bromo-2¹-amino - diphenylsulphide (m.p. 63° C.) used in this Example is obtained by reduction with stannous chloride or with iron of the corresponding nitro derivative (m.p. 111.5° C.), which is in turn prepared from 2-bromo-thiophenol and 2-chloro nitrobenzene.

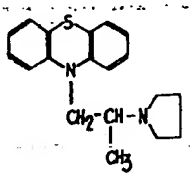
EXAMPLE IV.

1 - (10¹ - Phenthiazinyl) - propyl-3-*p*-toluene sulphonate (15 g.) and pyrrolidine (52 g.) are heated at 100° C. in an autoclave for 20 hours. After cooling, the excess pyrrolidine is driven off *in vacuo*. The residue, after the addition of water (35 cc.), is extracted with ether (50 cc. and then twice with 25 cc.). The ethereal extracts are shaken with normal hydrochloric acid (40 cc. and then twice with 15 cc.), and the combined acid extracts are decolorised with charcoal and then made alkaline with 10N caustic soda (7.5 cc.). The oily base which separates is then extracted with ether (3 lots of 50 cc.). After drying the ethereal extracts over sodium sulphate, the ether is driven off and the base so obtained is purified by conversion into the hydrochloride. There is thus obtained 10-(3¹-pyrrolidino-propyl)-phenthiazine hydrochloride (11.2 g.) which melts at 158° C.

The 1 - (10¹-phenthiazinyl)-propyl-3-*p*-toluene sulphonate is prepared by reacting *p-toluene* sulphonylchloride with 10-(3¹-hydroxypropyl)-phenthiazine.

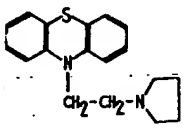
10-(3¹-Pyrrolidino - propyl)-phenthiazine and its salts have interesting pharmacodynamic properties, of which their anti-shock and hypotensive activities in particular are the most important, but they also have application in human or veterinary medicine by virtue of their properties of enhancing or prolonging the effect of anaesthetics and analgesics, and by reason of their anti-inflammation properties.

These various properties of 10-(3¹-pyrrolidino-propyl)-phenthiazine (designated as compound A) have been compared with those of compounds of related constitution which have already been described in the literature, for example 10-(2¹-pyrrolidino-propyl) - phenthiazine of the formula:



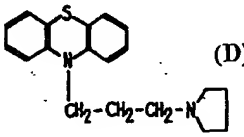
(B) (J.A.C.S. *70* 3100 (1948))

10-(2¹-pyrrolidinoethyl)-phenthiazine of the formula:



(C) (J.A.C.S. *70* 3100 (1948))

and 10-(3¹-piperidinopropyl) - phenthiazine of the formula:



(D) (J.A.C.S. *66* 891 (1944))

The tests, by means of which these various products have been compared, are described briefly below:—

(a) POTENTIATION OF ANAESTHETICS:—

HEXOBARBITONE

The substance to be studied is administered to the test animal (mouse) by the subcutaneous route in the dose of 20 mg/kg. Thirty minutes later hexobarbitone is administered by the intravenous route in the dose of 50 mg/kg. The mean duration of narcosis in minutes is noted, a control experiment being carried out at the same time on mice which have received hexobarbitone only.

ETHER

The product to be studied is administered to the test animal (mouse) by the subcutaneous route in the dose of 20 mg/kg. Thirty minutes afterwards the mice thus treated are placed in a bell jar in which a known quantity of ether is evaporated. When narcosis has been established the mice are removed from the jar and the duration of narcosis in free air is noted. As a control, mice which have not been treated with the substance under examination are placed in the ether jar at the same time.

(b) POTENTIATION OF ANALGESICS:

MORPHINE

Hesse' method—Arch. Exp. Path. Pharm. *158*, 233 (1930)—carried out on the mouse. The substance to be studied is administered in a dose of 20 mg/kg by the subcutaneous rout. Half an hour later morphine is administered in a dose of 5 mg/kg. also by the subcutaneous route, and the percentage of analgesia obtained in three hours is noted. A control experiment is carried out simultaneously on untreated mice.

(c) HYPOTHERMIC ACTIVITY

Tests with mice. The animals are placed in room at constant temperature (25° C.). The dose of the substance which produces a lowering of temperature of 5° when administered by the subcutaneous route is determined.

(d) ANTI-EMETIC ACTIVITY

The protection given by the test substances against vomiting in dogs produced by apomorphine is determined (G. Chen and Ch. Ensor—J. Pharmacol. *98* 245 (1950)). To do this the test substances are administered in a dose of 2 mg/kg. by the subcutaneous route 30 minutes before the injection of 0.1 mg/kg. of apomorphine also by the subcutaneous route (dogs are employed which have previously been found to be sensitive to the action of apomorphine). For each product the mean number of times that vomitting takes place during the 30 minutes following the injection of apomorphine is determined and from this the percentage reduction is calculated with reference to control animals.

(e) ANTI-SHOCK ACTIVITY.

Noble-Collip method—Quart. J. Exp. Physiol. *31*, 187 (1942). Shock is produced in rats by introducing them into horizontal metallic drums rotating about their axes at 40 revolutions per minute. Before introducing them into the drums, the rats receive subcutaneously in a known volume of solution 0.25, 0.5, 1 and 2.5 mg/kg. of the test substances. The mortality produced by a shock induced by 720 revolutions of the drums is noted. The controls receive subcutaneously the same volume of distilled water as the treated animals. The mortality of treated and untreated animals is compared.

The results obtained are summarized in the following table:

		Controls	A	B	C	D
Potentiation						
Duration narcosis minutes	Hexobarbitone	10	95	38	10	56
	Ether	2	24	5	2	20
% Analgesia 3 h.	Morphine	0	43	0	3	24
Hypothermia (−5°) dose mg/kg. s.c.			25	> 50		50
Anti-emetic activity % protection at 2 mg/kg. s.c.			69	58	45	33
Anti-shock—Noble-Collip						
Mortality	Doses mg/kg s.c. 0·25		6/48	8/11	10/12	5/12
	0·5		0/48	10/12	9/12	2/12
	1		1/48	10/12	10/12	0/12
	2·5		0/48	7/11	10/12	0/12
	Total	35/48	7/192	35/46	39/48	7/48
Mortality total %		72.9	3.6	76	81	14.5

It is clear from the results summarised in the above table that the substance A of the present invention is greatly superior from the pharmacodynamic point of view to the products of related constitution, identified above, which have already been described in the literature.

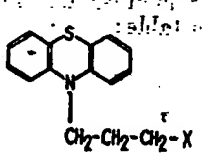
What we claim is:—

1. The compound 10-(3¹-pyrrolidinopropyl)-phenthiazine and its salts, including its quaternary ammonium salts.

2. Process for the preparation of the compound claimed in claim 1 or a salt thereof which comprises heating a 1-pyrrolidino-3-halogenopropane or salt thereof with phenthiazine.

3. Process according to claim 2 wherein the reaction is carried out in the presence of an alkaline condensing agent.

4. Process for the preparation of the compound claimed in claim 1 or a salt thereof which comprises heating pyrrolidine with a phenthiazine derivative of the formula:



where X represents the acid residue of an alkyl ester known to be active as an alkylating agent.

5. Process according to claim 4 wherein X is a halogen atom or a sulphonic or sulphuric ester group.

6. A process for the preparation of the compound claimed in claim 1 which comprises cyclising 2-bromo-2¹-(3¹¹-pyrrolidino-propyl)-amino-diphenyl sulphide by heating is in an anhydrous solvent in the presence of a basic condensing agent.

7. Process according to claim 6, wherein the basic condensing agent is an alkali metal carbonate and the cyclisation is effected in the presence of copper powder as catalyst.

8. A process for the production of 10-(3¹-pyrrolidinopropyl) - phenthiazine and salts thereof substantially as set forth in any one of the foregoing Examples.

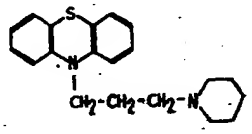
For the Applicants
J. A. KEMP & CO.,
Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1.

PROVISIONAL SPECIFICATION

Improvements in or relating to Phenthiazine Derivatives and to their producti n

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris 8e, France, do hereby declare this invention to be described in the following statement:—

This invention relates to new phenthiazine derivatives and to processes for their production. The new phenthiazine derivatives of the present invention are 10-(3¹-pyrrolidino-propyl) phenthiazine which has the formula:



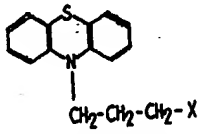
and its salts, including its quaternary ammonium salts.

Many processes have been described in the literature for the production of N-aminoalkyl phenthiazines and the present invention includes the production of the compounds specified above by any of such known methods, using the appropriate reagents.

In particular, the compound of the given formula may be obtained by any of the following methods:

(a) By the action of a 1-pyrrolidino-3-halogenopropane (in the form of the base or a salt thereof) on phenthiazine. This condensation may be carried out without a condensing agent by the action of a solution, for example in xylene, of the 3-pyrrolidino-1-halogenopropane base on molten phenthiazine. It is, however, preferred to operate in the presence of an alkalin condensing agent, e.g. an alkali metal or derivative thereof such as the hydroxides, hydrides, amides or alcoholates, and more particularly sodium or sodamide, in solution in an organic solvent, (e.g. toluene or xylene) at the boiling point of the solvent.

(b) By the action of pyrrolidine on a phenthiazine of the formula:



in which X represents a halogen atom or the residue of a sulphonic or sulphuric ester.

(c) By the ring-closure, by treatment with an alkali metal carbonate in the presence of copper powder as catalyst, of 2-bromo - 2¹ - (3¹¹ - pyrrolidino - propyl)-amino-diphenylsulphide.

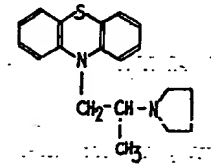
The following Example will serve to illustrate the invention:—

EXAMPLE.

A solution of 3-pyrrolidino-1-chloropropane (23.6 g.) in xylene (50 c.c.) is run gradually over a period of ½ hour with agitation into a mixture of phenthiazine (26.5 g.), sodamide (85%; 7.8 g.) and xylene (100 c.c.), heated to 110° C. When the addition has been completed, heating is continued for a further 2 hours at about 140° C. After cooling, the reaction mixture is treated with water (200 c.c.) and made acid to methyl orange with hydrochloric acid (d=1.16; 25 c.c.). The xylene layer is separated and the aqueous layer is extracted with ether (100 c.c.). The ether is decanted and the aqueous layer is then made alkaline to thymolphthalein with sodium hydroxide (d=1.33; 25 c.c.). The base is extracted with ether (3×100 c.c.). The ethereal solution is dried over sodium sulphate, the ether is evaporated on the water-bath and the residue is distilled. 10-(3¹-pyrrolidino - propyl)-phenthiazine (35 g.) is thus obtained which boils at 210—220° C. under 0.45 mm. of mercury. By treating the base dissolved in acetone with an acetone solution of oxalic acid, the acid oxalate is obtained which melts at 190° C. (Kofler). By treating the base dissolved in acetone with methyl iodide, the iodomethylate is obtained which, after recrystallisation from alcohol, melts at 196—198° C. (Kofler).

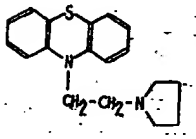
10-(3¹-Pyrrolidino-propyl) - phenthiazine and its salts have important pharmacodynamic properties, of which their anit-shock activity in particular is one of the most interesting, but they may also be used in human or veterinary therapeutics by virtue of their properties of potentiating anaesthetics and analgesics, and by reason of their anti-inflammation properties.

These various properties of 10-(3¹-pyrrolidino-propyl)-phenthiazine (designated as compound A) have been compared with those of compounds of related constitution which have already been desribed in the literature, for example, 10-(2¹-pyrrolidino-propyl) - phenthiazine of the formula:



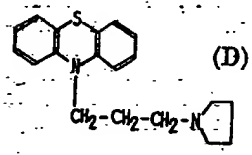
(B) (J.A.C.S. *70* 3100 (1948))

10-(2¹-pyrrolidinoethyl)-phenthiazine of the formula:



(C) (J.A.C.S. *70* 3100 (1948))

and 10-(3¹-piperidinopropyl) - phenthiazine of the formula:



(D) (J.A.C.S. *66* 891 (1944))

The tests, by means of which these various products have been compared, are described briefly below:

(a) POTENTIATION OF ANAESTHETICS:—

HEXOBARBITONE

The substance to be studied is administered to the test animal (mouse) by the subcutaneous route in the dose of 20 mg/kg. Thirty minutes later hexobarbitone is administered by the intravenous route in the dose of 50 mg/kg. The mean duration of narcosis in minutes is noted, a control experiment being carried out at the same time on mice which have received hexobarbitone only.

ETHER

The product to be studied is administered to the test animal (mouse) by the subcutaneous route in the dose of 20 mg/kg. Thirty minutes afterwards the mice thus treated are placed in a bell jar in which a known quantity of ether is evaporated. When narcosis has been established the mice are removed from the jar and the duration of narcosis in free air is noted. As a control, mice which have not been treated with the substance under examination are placed in the ether jar at the same time.

(b) POTENTIATION OF ANALGESICS:

MORPHINE

Hesse's method — Arch. Exp. Path. Pharm. *153*, 233 (1930)—carried out on the mouse. The substance to be studied is administered in a dose of 20 mg/kg by the subcutaneous route. Half an hour later morphine is administered in a dose of .5 mg/kg also by the subcutaneous route, and the percentage of analgesia obtained in three hours is noted. A control experiment is carried out simultaneously on untreated mice.

(c) HYPOTHERMIC ACTIVITY

Tests with mice. The animals are placed in room at constant temperature (25° C.). The dose of the substance which produces a lowering of temperature of 5° when administered by the subcutaneous route is determined.

(d) ANTI-EMETIC ACTIVITY

The protection given by the test substances against vomiting in dogs produced by apomorphine is determined (G. Chen and Ch. Ensor—J. Pharmacol. *98*, 245 (1950)). To do this the test substances are administered in a dose of 2 mg/kg. by the subcutaneous route 30 minutes before the injection of 0.1 mg/kg. of apomorphine also by the subcutaneous route (dogs are employed which have previously been found to be sensitive to the action of apomorphine). For each product the mean number of times that vomitting takes place during the 30 minutes following the injection of apomorphine is determined and from this the percentage reduction is calculated with reference to control animals.

(e) ANTI-SHOCK ACTIVITY

Noble-Collip method—Quart. J. Exp. Physiol. *31*. 187 (1942). Shock is produced in rats by introducing them into horizontal metallic drums rotating about their axes at 40 revolutions per minute. Before introducing them into the drums, the rats receive subcutaneously in a known volume of solution 0.25, 0.5, 1 and 2.5 mg/kg of the test substances. The mortality produced by a shock induced by 720 revolutions of the drums is noted. The controls receive subcutaneously the same volume of distilled water as the treated animals. The mortality of treated and untreated animals is compared.

The results obtained are summarized in the following table:

		Controls	A	B	C	D
Potentiation						
Duration narcosis minutes	Hexobarbitone	10	95	38	10	56
	Ether	2	24	5	2	20
% Analgesia 3 h.	Morphine	0	43	0		24
Hypothermia (−5°) dose mg/kg. s.c.			25	> 50		50
Anti-emetic activity % protection at 2 mg/kg. s.c.			69	58		33
Anti-shock—Noble-Collip						
Mortality	Doses mg/kg s.c. 0.25		6/48	8/11		5/12
	0.5		0/48	10/12		2/12
	1		1/48	10/12		0/12
	2.5		0/48	7/11		0/12
	Total	35/48	7/192	35/46		7/48
Mortality total %		72.9	3.6	76		14.5

It is clear from the results summarised in the above table that the substance A of the present invention is greatly superior from the pharmacodynamic point of view to the products of related constitution, identified above, which have already been described in the literature.

For the Applicants,
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